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redakcja@pediatricendocrinology.pl
www.pediatricendocrinology.pl
www.pteidd.pl

Familial hypercholesterolemia – treatment update in children, systematic review

Rodzinna hipercholesterolemia – podsumowanie leczenia u dzieci, przegląd literatury

[1]Sabina Ziółkowska, [1]Noëlle Kijek, [1]Iga Zendran, [1]Ewa Szuster, [2]Ewa Barg

[1]Graduate of Wroclaw Medical University, Poland
[2]Department of Basic Medical Sciences, Wroclaw Medical University, Poland

Abstract
Familial hypercholesterolaemia is one of the most common genetic diseases, and its first symptoms occur in childhood. Proper diagnosis and treatment prevent young patients from severe consequences in their future. The treatment of this dyslipidaemia is still evolving, and new promising agents are being discovered. In this review we summarize the old and new treatment methods of familial hypercholesterolaemia, giving an update estimated on the latest publications.
Key words:
hypercholesterolaemia, children, adolescents, hyperlipoproteinaemia, cholesterol.

Streszczenie
Rodzinna hipercholesterolemia jest jedną z najczęstszych chorób o podłożu genetycznym, a jej pierwsze objawy pojawiają się już w dzieciństwie. Właściwie postawiona diagnoza i leczenie może uchronić młodych pacjentów przed poważnymi konsekwencjami zdrowotnymi w przyszłości. Sposoby leczenia tej dyslipidemii ewoluują i pojawiają się nowe obiecujące leki. W pracy podsumowano już znane oraz nowe metody leczenia rodzinnej hipercholesterolemii, dokonując przeglądu najnowszej literatury.
Słowa kluczowe:
hipercholesterolemia, dzieci, młodzież, hiperlipoproteinemia, cholesterol.

Introduction

Dyslipidaemias are defined as abnormal lipid and lipoprotein concentrations. This disorder may be caused by genetic factors (primary dyslipidaemia) or environmental factors (secondary dyslipidaemia) such as a diet enriched with animal fats, physical activity, social factors, smoking, alcohol, etc [1]. Among primary dyslipidaemias we can distinguish familial hypercholesterolaemia, familial defective apolipoprotein B-100, and familial lipoprotein lipase deficiency. Secondary dyslipidaemias co-exist with type 1 and 2 diabetes, hypothyroidism, obesity, and liver and kidney diseases, such as chronic renal failure, nephrotic syndrome, and chronic liver inflammation [2].

In dyslipidaemia we can differentiate 3 types of lipid abnormalities: hypercholesterolaemia, atherogenic dyslipidaemia, and hypertriglyceridaemia. Hypercholesterolaemia is defined as elevated triglycerides ≥ 190 mg/dl (≥ 5.0 mmol/l) or elevated concentration of LDL-C (low-density lipoproteins). It should be considered that in the paediatric population normal values of the lipid profile are lower; LDL-C levels should be <110 mg/dl and the triglyceride level should be < 75 mg/dl among children younger than 9 years old and <90 mg/dl among children above 9 years old. Atherogenic dyslipidaemia refers to increased level of triglycerides above 150 mg/dl (≥ 1,7 mmol/l), decreased level of HDL-C: < 40 mg/dl (< 1 mmol/l) in men and < 48 mg/dl (< 1.2 mmol/l) in women and the presence of small dense low-density lipoprotein in plasma. Among the paediatric population HDL-C levels should be higher than 45 mg/dl. Hypertriglyceridaemia is described as an elevated level of triglycerides in plasma > 150 mg/dl (> 1.7 mmol/l), while the concentration of LDL-C is correct. In a severe hypertriglyceridaemia, the concentration of triglycerides levels are above 800 mg/dl (≥ 9 mmol/l) [1, 3].

Dyslipidaemias are common disorders of lipoprotein metabolism, which lead to a number of abnormalities such as elevated total cholesterol, elevated low-density lipoprotein, as well as non-high-density cholesterol, triglycerides, and lowered high-density lipoproteins [4]. Those are followed by atherosclerosis and lead to cardiovascular diseases, which are the leading cause of death worldwide [5]. Although cardiovascular diseases are not observed in children, the risk factors occur, and they remain silent until adulthood [6]. Clinical data and evidence clearly show that atherosclerosis begins in childhood [7]. It has been observed that half of children with an ab-

Ewa Szuster
e-mail: ewa.szuster8@gmail.com

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normal concentration of TC (total cholesterol) or LDL-C level (above the 75th percentile) remained elevated in adulthood [8].

Familial hypercholesterolaemia (FH) is a hereditary disorder that may lead to premature cardiovascular diseases, and it is considered the most common monogenic disease [9]. It is characterized by mutations in genes encoding proteins involved in lipoprotein metabolism, mainly the mutation in genes coding the LDL receptor, B apolipoprotein, or PCSK9 [10]. This mutation leads to an increased level of low-density lipoprotein from the beginning of the patient's life. Homozygous familial hypercholesterolaemia in children, which affects one in a million individuals worldwide, may cause serious coronary heart disease in the first decade of life [11, 12]. Moreover, these young patients often die of myocardial infarction before the age of 20 years [13, 14]. Heterozygous familial hypercholesterolaemia affects 1 per 250 persons, and it is estimated that worldwide 6.8-8.5 million children and adolescents could suffer from this disease [15]. In every patient under 20 years of age with elevated levels of LDL (above 160 mg/dl), familial hypercholesterolaemia should be taken into consideration [16].

In people suffering from familial hypercholesterolaemia, atherosclerosis affects mainly the aortic root, the ascending and descending aorta, but also the peripheral vessels – the femoral and renal arteries [17]. Also, it has been observed in non-invasive imaging in children with familial hypercholesterolaemia that the thickness of the carotid intima-media is significantly greater compared with control children in 9 studies [18]. Lipid depositions in those patients may also be found in the eye, the skin, and the tendons. Homozygous phenotypes present xanthomas both in tendons and skin, but heterozygous usually in tendons only. What is very characteristic for this disease is the thickening of the Achilles tendons. It may lead to inflammation and be painful for the patient. Other lesions characteristic for patients with familial hypercholesterolaemia, but less specific, are cutaneous xanthelasma of the eyelids. The detection of xanthomas or arcus corneae in clinical examination may indicate a higher risk of cardiovascular events [17].

Diagnostics

The diagnosis of hypercholesterolaemia is based on medical history and physical, laboratory, and genetic examinations, depending on the age of the patient.

In adults, it is recommended that routine lipid profile testing be performed in all men over 40 years of age, and for women over 50 years of age or having gone through the menopause [19]. Also it is recommended that the examination be performed in people who have symptoms like tendon xanthoma or/and eyelid xanthoma or degeneration of corneal lipidosis, as well as counselling for people suffering from hypertension, obesity, diabetes, autoimmune diseases, high cardiovascular risk, or established diseases of the cardiovascular system [19].

In children, the referral for lipid testing is slightly different. It focuses on examining patients with a positive family history of dyslipidaemia or premature atherosclerotic or premature cardiovascular diseases [4, 20]. Usually the screening start at the age of 2 years, due to the fact that during the first months of life a lot of fluctuations in cholesterol levels are noted [21, 29]. It is also worth referring to obese children (> 97th percentile), hypertensive (≥ 95th percentile), diabetic, pregnant, or smoking [20]. For children without any cardiovascular disease (CVD) risk factors, the first screening towards familial hypercholesterolaemia should be performed between 9 and 11 years of age [4, 22, 29]. Between the age of 12 and 21 years screening due to the lipid changes is not recommended for those without any CVD risk factors, because lipid changes may occur during puberty, increasing the possibility of false-negative results [4,23]. In the first step, it is necessary to exclude secondary hyperlipidaemia, which may appear in the course of: hypothyroidism, kidney disease, liver disease, diabetes, or the use of drugs (e.g. glucocorticosteroids, antiepileptics) [4].

When referring the patient for a lipid profile, the concentration of total cholesterol, HDL-C, and triglycerides should be measured, and LDL-C should be determined using the Friedewald formula (valid only if the triglyceride level is lower than 400 mg/dl (<4.5 mmol/l), if more direct LDL should be measured and non-HDL cholesterol [16, 23].

Friedewald formula:

LDL = TC – (HDL + TG/2,2) (mmol/l)

LDL = TC – (HDL + TG/5) (mg/dl).

The test should be performed after 6-hour fasting, which can be difficult in children. Nevertheless, studies show that fasting does not significantly affect TC, LDL, and HDL levels and would not be necessary in screening tests. Only the concentration of triglycerides differed more significantly on the basis of fasting status [24]. According to the European guidelines, the measurement of lipoprotein should be performed once in the life of each person. It is also recommended that apoB be measured for risk assessment, especially in people with elevated triglycerides, diabetes mellitus, obesity, or very low LDL-C levels [19].

In children, the values of the lipid profile can be divided into acceptable, borderline, and abnormal (Table I). A sensitive screening test for dyslipidaemia or predicting increased carotid intima-media thickness in children seems to be non-fasting non-HDL-C level [25].

Acceptable, borderline, and abnormal lipid and lipoproteins serum concentrations for children and adolescents are presented in Table I [1, 4, 29].

A disturbance in the lipidogram in adults is the posture of suspicion of familial hyperlipidaemia. Lipid disorders are listed below [4, 26, 27, 29]:

- Fasting triglyceride level:
  - normal: < 75 mg/dl (< 9 years old), < 90 mg/dl (≥ 9 years old),
  - mile: 75–100 mg/dl (< 9 years old), 90-130 mg/dl (≥ 9 years old),
  - high: >100 mg/dl (< 9 years old), > 130 mg/dl (≥ 9 years old);
- LDL-C level:
  - optimal: < 100 mg/dl,
  - near optimal: 100–129 mg/dl,
  - borderline high: 130–159 mg/dl,

Table I. Acceptable, borderline and abnormal lipid and lipoproteins serum concentration for children and adolescents [1, 4, 29]

Categories	TC (mg/dl)	LDL (mg%)	Non-HDL (mg/dl)	HDL (mg/dl)	TG < 9 y. (mg/dl)	TG ≥ 9 y. (mg/dl)	Percentile
Acceptable	< 170	< 110	< 123	> 45	< 75	< 90	< 75
Borderline	170–199	110–129	123–143	45–35	75–100	90–129	75–95
Abnormal	> 200	> 130	> 143	< 35	> 100	> 130	> 95

TC – total cholesterol, LDL – low density lipoprotein, Non-HDL – non-high density lipoprotein, HDL – high density lipoprotein, TG ≥9y. – triglycerides among patients older 9 years old, TG<9 y. – triglycerides among patients below 9 years old

– high: 160–189 mg/dl,
– very high: > 190 mg/dl;
- HDL level:
  – low: < 40 mg/dl,
  – high: > 60 mg/dl.

If the values of total cholesterol and its fractions are within the reference range, it is indicated to repeat the lipid profile every 3 to 5 years [19]. In children, the lipid profile should be performed twice with an interval of 2-3 weeks to calculate the mean value [28, 29]. In the case of abnormalities, another examination should be performed within 3 weeks to confirm, and then the treatment should be started. The lipid profile should not be examined earlier than 3 months after an acute infectious disease [28].

Genetic tests are also used for diagnostics. In the population, familial heterozygous appears to be (HeFH) about 1 in 200–250, family homozygous (HoFH) up to 1 in 160 000–320 000, mixed form 1 in 100/200, or less common (such as familial lipoprotein lipase deficiency, familial chylomicronaemia syndrome, familial dysbetalipoproteinaemia, or familial lecithin-cholesterol acyltransferase deficiency (LCAT)) [19].

So far 3 genes have been established [10, 26, 28, 29]:
- *LDL receptor* gene (the most common cause),
- *apoB* gene,
- *subtilisin/kexin proprotein convertase type 9* gene (PCSK9, proprotein convertase subtilisin kexin 9).

High cost and limited availability limit the number of executions of the test. It is recommended to perform genetic testing in humans when the serum total cholesterol level exceeds 310 mg/dl (≥ 8 mmol/L), in an adult patient or a family member, premature coronary artery disease in a patient or his/her family member, xanthoma tendons in a patient or a family member, sudden cardiac death at an early age in a family member, in children with a positive family history of dyslipidaemia or premature atherosclerotic or premature cardiovascular diseases presenting lipidogram abnormalities [23–26]. Cascade diagnosis of relatives of the identified proband based on triglycerides or LDL-C concentration or the presence of mutations confirmed by genetic testing (if the test was performed) is the most effective way to identify new FH cases. Under current recommendations, genetic testing can make diagnosis much easier and faster, but is not necessary for diagnosis. They also cannot constitute a criterion for possible therapeutic programs or reimbursement because they will thus limit the availability of modern treatment. Various criteria have been developed to determine the likelihood of familial hyperlipidaemia for adults such as the following: Dutch criteria (Table II), Simon Broome criteria (Table III) (United Kingdom), and MEDPED criteria (USA). Usually the criteria of the Dutch Lipid Clinic Network and Simon Broome Register [2, 9, 16, 19] are used because they are better adapted to the Polish population [16]. Based on these criteria, the disease can be diagnosed with a high probability. For the Polish paediatric population, most useful is the scheme from the United Kingdom [28, 29] because it does not contain clinical symptoms in the proband, which in the form of heterozygote are not seen in children [19]. Additionally, adult risk assessment scores, which were developed based on the CVD risk in the general population, should not be used in individuals with heterozygous familial hypercholesterolaemia who have a lifetime risk for CVD events [4]. After making an appropriate diagnosis, it is necessary to immediately start lipid-lowering treatment, preferably in a specialized centre.

Management and therapy goals

A multidisciplinary approach is required in FH treatment in paediatric patients, including supervision by a paediatric diabetologist/endocrinologist, clinical geneticist, clinical dietitian, and preferably a psychologist. When FH is diagnosed, introducing proper education, physical activity, dietary intervention, and pharmacological treatment is necessary, because only all these elements combined may provide a long-term favourable outcome and result in reduction of total cardiovascular risk [28]. To achieve optimal compliance in a young patient, all members of the family should be involved in the process. The main therapy goal is to reduce the LDL-C blood level by 50% or LDL-C below 130 mg/dl. Among diabetic patients the main therapy goal is to keep non-HDL cholesterol level below 130 mg/dl (3.36 mmol/l) and LDL cholesterol lower than 100 mg/dl (2.59 mmol/l) [29,30].

Table II. Dutch Criteria [12]

Criteria	Points
Family history	
First-degree relative with known premature* coronary and vascular disease	1
Plasma LDL-C > 95th percentile for age and sex in an adult relative	1
Plasma LDL-C > 95th percentile for age and sex in an relative < 18 years of age.	2
Tendon xanthomata and/or arcus cornealis	2
Clinical history	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels mg/dl (mmol/liter)	
LDL-C ≥ 330 mg/dl (≥ 8.5)	8
LDL-C 250–329 mg/dl (6.5–8.4)	5
LDL-C 190–249 mg/dl (5.0–6.4)	3
LDL-C 155–189 mg/dl (4.0–4.9)	1
DNA analysis	
Functional mutation in the *LDLR*, *apo B* or *PCSK9* gene	8
Diagnosis (diagnosis is based on the total number of points obtained	
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6–8
Possible familial hypercholesterolemia	3–5
Unlikely familial hypercholesterolemia	< 3

* Premature < 55 years in men; < 60 years in women LDL-C – low density lipoprotein cholesterol; FH – familial hypercholesterolemia; LDLR – low density lipoprotein receptor; Apo B – apolipoprotein B; PCSK9 – Proprotein convertase subtilisin/kexin type 9

Table III. Simon Broome Criteria [12, 21]

Points	Criteria
1	Total cholesterol levels > 290 mg/dl (> 7,5 mmol/l) or LDL-C >190 mg/dl (4.9 mmol/l) in adults. Total cholesterol levels > 260 mg/dl (> 6.7 mmol/l) or LDL-C > 155 mg/dl (4.0 mmol/l)
2	Tendon xanthomas in the patient or tendon xanthomas in a first or second degree relative
3	DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation
4	Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative
5	Family history of elevated total cholesterol > 290 mg/dl (> 7.5 mmol/l) in an adult first or second-degree relative
6	Family history of elevated total cholesterol > 260 mg/dl (6.7 mmol/l) in a child, brother or sister 16 years or younger
Diagnosis	
Definite familial hypercholesterolemia = 1 + 2 or 3	
Possible familial hypercholesteremia = 1 + 4 or 5	

LDL-C – low density lipoprotein cholesterol; Apo B – apolipoprotein B; PCSK9 – Proprotein convertase subtilisin/kexin type 9

Non-pharmacological treatment

Lifestyle modifications such as increased physical activity – walking, running, swimming, cycling, introduction of low-fat diet, which should include whole grain food, lean meat, fruits, vegetables, and reduction of salt, sugar, and saturated fat intake – are essential in FH management [31]. Sedentary lifestyle should be strongly discouraged, and an adequate amount of daily sleep should be provided because recent observations have proven that these factors correlate with lipid profile alterations [32]. Despite the fact that a healthy diet is a necessity, it is nowadays regarded more as an integral part of the whole treatment process rather than a sufficient method itself, as it used to be in the past, when 6 to 12 months of diet therapy were recommended before introducing pharmacotherapy [28,33]. Such management is, however, still suggested by some experts. Dietary intervention is safe for children from the age of 2 years and routinely recommended for such patients [1,34,35]. However, the Special Turku Coronary Risk Factor Intervention Project (STIRP) and Dietary Intervention Study in Children (DISC)

have proven the low-fat diet to be safe even after the age of 7 months, and therefore it may be recommended from this age when necessary, but only under medical supervision [36]. Current dietary recommendations for paediatric patients with lipid profile disturbances, formed by the European Atherosclerosis Society (EAS) Consensus Panel and National Heart, Lung, and Blood Institute (NHLBI), suggest that daily intake of cholesterol should not exceed 200 mg, and no more than 7% of consumption of daily calories should come from saturated fat and 30% from fat in general [1,33]. The suggested diet should be based on vegetables, fruit, fish, lean meat, low-fat dairy, and whole grain products, with a possible addition of plant sterols/stanols in children from the age of 6 years [1,37]. Plant sterols/stanols have been proven to lower the LDL-C by an additional 9-19%, compared to a low-fat diet only [38]. Data on the addition of omega-3 acids is inconclusive and as yet has no proven impact on LDL-C levels in FH patients. As mentioned before, dietary intervention should involve the whole family for better compliance [15,39]. Daily moderate physical activity and vigorous activity 3 days per week is also recommended in children from the age of 5 years due to its positive impact on fasting LDL-C level as well as other cardiovascular risk factors: blood pressure, glucose blood level, and BMI [1,40]. However necessary, lifestyle modifications may be challenging for young patients and are not as beneficial in children with FH as they are in secondary dyslipidaemias such as obesity-related lipid alterations [39,41]. Therefore, pharmacological therapy appears to play a crucial role in FH treatment.

Pharmacotherapy

Statins

Statins are the agents of first choice in FH treatment among children older than 8 years [1,30,42]. Their mechanism of action includes inhibition of HMG CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase, an enzyme indispensable in endogenous cholesterol production, which triggers the upregulation of cell surface LDL receptors and eventually results in increased LDL particle clearance and therefore lowers the blood LDL-C level by approximately 33.8% [43]. Statin administration also results in reduction of triglyceride level and an increase in HDL-C level [43]. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have approved simvastatin, rosuvastatin, lovastatin, and atorvastatin for safe use in patients older than 10 years. Pravastatin at doses up to 4 mg has been approved in children after the age of 8 years by the FDA, and rosuvastatin – after the age of 6 years by the EMA. Placebo-controlled studies have also proven pitavastatin safe and well tolerated in patients aged 6 years and over [44]. Pharmacotherapy with statins should generally be introduced in paediatric patients at diagnosis from the age of 8-10 years, as stated in the recommendations [1,30,33]. Other risk factors, such as family history, coexisting diseases, or metabolic disorders must also be taken into consideration in the decision-making process. Statin therapy is currently recommended in paediatric patients with an LDL-C level ≥190 mg/dl (4.91 mmol/l). In patients with at least 2 additional risk factors of CVD (such as hypertension, obesity, or smoking) or diabetes, therapy is recommended from an LDL-C level equal to or above 160 mg/dl (4.14 mmol/l) and 130 mg/dl (2.59 mmol/l), respectively. In certain cases, initiation of therapy earlier than at the age of 8 years may be substantiated, as in the case of homozygous familial hypercholesterolaemia (HoFH) with LDL-C level > 500 mg/dl (12.93 mmol/l), where treatment may be necessary as early as at the age of 2 years, and a more aggressive approach is needed [29, 30]. In heterozygous familial hypercholesterolaemia (HeFH) statin administration should be initiated at the lowest possible doses, with following slow dosage increase by 1 increment (10 mg) if the LDL-C target levels are not achieved within at least 3 months, up to a desired LDL-C target [1]. Therapeutic effects noticeable after 2 weeks correspond with about 90% of the full effect, which may be observed after approximately 6 weeks [28, 45]. Creatine kinase and hepatic aminotransferases should be checked before the implementation of the statin therapy. Therapy monitoring includes annual monitoring of body mass, body measurements as well as a glycated haemoglobin (HbA1c) every 6 months and hepatic aminotransferases every 3 months. LDL-C levels as well as general growth and the puberty pattern should also be observed [33, 46]. Plasma creatine phosphokinase (CPK) should be measured only when myopathy symptoms occur; routine monitoring is not recommended. Routine IMT measurement in carotid ultrasound is also not included in the current recommendations [33]. Statins are generally well tolerated in paediatric patients, with few side effects such as gastrointestinal disorders, headache, fatigue, and very rarely neuropathy and rhabdomyolysis. They exhibit variable lipid-lowering efficacy depending on the agent and dosage [43]. Most data concerning statin therapy in children refers to short-term interventions [44, 47–52]. As of today, only a few studies take into account its possible long-term outcome and safety profile [53–55]. Nevertheless, to the best of our knowledge these are rather favourable - a recently published 20-year follow up study including 214 paediatric patients showed that statin therapy initiated during childhood and adolescence (mean age of 14 years) significantly reduces the risk of a cardiovascular disease in adulthood with no negative impact on growth and pubertal development [55]. Although statin therapy is beneficial for most paediatric patients, some of them may require additional agents to attain LDL-C goals [56,57]. Such an approach is often necessary in HoFH patients at diagnosis.

Ezetimibe

Ezetimibe acts as a selective cholesterol absorption inhibitor by blocking the Niemann-Pick C1-like intracellular cholesterol transporter1 (NPC1L1) at the enterocyte brush border. By reducing cholesterol uptake in the small intestine, its administration eventually results in a reduction of total cholesterol, LDL-C, Apo-B, and TG levels and an increase in HDL-C levels in patients with hypercholesterolaemia. Because its mechanism of action differs from that of HMG-CoA reductase inhibitors, ezetimibe may be effectively combined with statin therapy, resulting in a decrease of LDL-C plasma level by an additional

10–15% [58]. It is the most frequently used second-line lipid-lowering agent in FH patients [59]. Combined statin and ezetimibe therapy has been shown to reduce LDL-C levels by approximately 69% in recent studies concerning paediatric FH patients [60]. Maximal response is usually achieved within 2 weeks of treatment [29]. Ezetimibe is approved for use in children from the age of 10 years both in Europe and in the USA. It is generally well tolerated and has a relatively low incidence of adverse events, most commonly digestive disorders. The adverse effects are at a similar level regardless of whether administered alone or combined with statin therapy [58, 61]. Ezetimibe is also considered the agent of first choice in patients with statin intolerance and a valuable addition to statins and apheresis in HoFH management [62].

Bile acid sequestrants

Bile acid sequestrants (BAS), also known as resins, may reduce LDL-C plasma level by 10–20% in the mechanism of binding bile acids in the intestinal lumen, which causes lower reabsorption of the above-mentioned. Because they are not systemically absorbed, these agents were once considered the only suitable treatment for hypercholesterolaemia in children [63]. Not only do resins tend to have frequent and unpleasant adverse effects, mostly gastrointestinal disorders, which significantly worsens the long-term patient adherence, but they also affect the absorption of fat-soluble vitamins (A, D, E, K) and folates in the small intestine [64]. All that combined makes the classic BAS rather a marginal treatment modality for hypercholesterolaemia in paediatric patients at present [1]. A promising alternative may be found in a second-generation agent, colesevelam, which has much stronger affinity to bile acids than the classic BAS and therefore may be used in lower dosage and trigger fewer adverse effects [65, 66]. The agent may be administered in monotherapy or safely combined with classic statin therapy. However, colesevelam is not commonly used in Europe; it is approved only for patients from the age of 10 years by the FDA at this point.

Other agents

Fibric acid derivatives (fibrates) are generally well tolerated but currently not commonly administered in paediatric patients with FH. However, they may be useful in children with hypertriglyceridaemia because they are able to reduce blood TG levels by up to 40–60% [1, 67]. Niacin is not recommended for routine use in paediatric FH patients due to frequent adverse effects, such as headache, flushing, liver failure, myopathy, and impaired glucose tolerance, and because of limited experience in this age group [15, 31].

Novel agents

Mipomersen

Mipomersen acts as an antisense oligonucleotide inhibitor of apolipoprotein B (apo-B), resulting in an additional decrease in VLDL-C and LDL-C of up to 36% [68, 69]. It was approved by the FDA as an orphan drug for HoFH and severe HeFH patients, both from the age of 12 years. The EMA, however, refused marketing authorisation for this agent due to adverse events outweighing the benefits of its administration and resulting in poor compliance [70].

Lomitapide

Lomitapide is an inhibitor of microsomal triglyceride transfer protein (MTP), which plays an essential role in the formation of hepatic and intestinal apoB-containing lipoproteins [71]. Adverse effects, mostly gastrointestinal, are manageable and the effectiveness in paediatric patients is promising – LDL-C levels decreased by approximately 58.4%, as shown in a recent treatment outcome study [72]. The agent was approved by both the EMA and FDA as an orphan drug for HoFH, but only in adult patients as yet. Clinical trials in paediatric patients from the age of 7 years are being conducted (NCT04681170).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

Evolocumab and alirocumab are monoclonal antibodies, both acting as inhibitors of the proprotein convertase subtilisin/kexin type 9 (PCSK9), a protease leading to LDL-R degradation. By reducing PCSK9 activity, their administration results in enhanced expression of LDL receptors on the hepatic cell surface and thus increases LDL-C catabolism [73, 74]. Evolocumab was shown to reduce LDL-C serum levels by approximately 44.5% at week 24 in HeFH patients aged from 10 to 17 years in a randomized, double-blind, placebo-controlled trial [75]. It was also shown to be well tolerated and efficient in children with HoFH [76]. Alirocumab demonstrated a similar safety profile and treatment outcome, but more research is still needed before its approval in this age group [77]. They both are administered subcutaneously, and the most frequent side effects include erythema at the injection site, nasopharyngitis, and headache. PCSK9 inhibitors are a promising alternative for patients from the age of 12 years, who are statin intolerant or resistant to conventional statin-ezetimibe treatment [78]. A similar agent, inclisiran, acting as a *PCSK9* gene-silencing drug via small interference RNA, is under evaluation with promising effects, also in paediatric patients with HoFH (NCT04659863) and HeFH (NCT04652726) [79].

Evinacumab

Evinacumab is a fully human monoclonal antibody targeted at angiopoietin-like 3 (ANGPTL3) and resulting in reducing its activity. ANGPTL3 acts as an inhibitor of lipoprotein and endothelial lipase. The loss-of-function variant and pharmacologic inhibition of ANGPTL3 reduces LDL-C levels via an LDL-receptor independent mechanism [80–82]. Evinacumab has been proven to significantly reduce LDL-C levels even in difficult-to-treat HoFH patients with little to no LDL-receptor activity, who did not respond to prior aggressive treatment including statins, ezetimibe, Lomitapide, and PCSK9 inhibitors. The mean LDL-C level decrease reached 47.1% in the ELIPSE-HoHF Study at 24 weeks of evinacumab treatment [83]. A significant LDL-C reduction by an additional 50% has also been shown in patients

with HeHF and treatment-resistant hypercholesterolaemia in recent studies [84]. The overall tolerance of the agent is good, with no serious adverse events observed during therapy. The most common side effects included headache, nasopharyngitis, and erythema at the site of injection. In February 2021, evinacumab was registered by the FDA for the treatment of HoFH patients from the age of 12 years [85]. Clinical trials are already in progress for children with HoFH aged from 5 to 11 years (NCT04233918). The agent may represent a long-awaited advance in the management of treatment-resistant HoFH and HeFH patients.

Lipoprotein apheresis

LDL apheresis (LDL-A) may act as an effective treatment method, especially in patients with homozygous FH (HoFH), in which pharmacotherapy is often not sufficient to lower plasma LDL-C to a desired level. The apheresis technique consists of selective removal of LDL particles from the bloodstream by binding them to dextran sulphate or polyacrylamide filter membrane, resulting in up to 70% LDL-C level reduction immediately after the procedure [15, 86]. Although effective, selective apheresis is time-consuming, expensive, and only temporary, requiring a repeat procedure every 1-2 weeks [87]. At this point, there are only limited data on the long-term effects of selective LDL-A in paediatric patients [88-90]. Cases reported so far have, however, proven the method to be remarkably efficient and safe, with no negative impact on growth and puberty. It should be considered in patients as early as at the age of 5 years and initiated no later than at the age of 8 years [91].

Conclusions

Despite being the most common metabolic genetic disorder, FH is still underrecognized and undertreated. Emphasis should be given to early diagnosis. A multidisciplinary, family-centric approach should also be introduced as soon as possible because studies show that treatment at an early stage significantly reduces future CVD risks in paediatric patients. Novel therapeutic options, including monoclonal antibodies, may be regarded as a great advance in paediatric FH treatment; however, further large, long-term trials are necessary in order to establish their safety profile and prolonged effects.

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